PATENT
Attorney Docket No.: 015280-462100US
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

SHOEMAKER et al.

Application No.: 10/528,747

Filed: March 22, 2005

For: IDENTIFICATION OF ANTI-HIV COMPOUNDS INHIBITING VIRUS ASSEMBLY AND BINDING OF NUCLEOCAPSID PROTEIN TO NUCLEIC ACID

Customer No.: 45115

Confirmation No. 1785

Examiner: Stuart Snyder

Technology Center/Art Unit: 1648

DECLARATION UNDER 37 C.F.R. § 1.132 BY DR. ROBERT SHOEMAKER

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Robert H. Shoemaker, currently hold the position of Chief, Screening Technologies Branch, Developmental Therapeutic Program at the National Cancer Institute at Frederick, Maryland. I am a co-inventor of the subject matter disclosed and claimed in the above-referenced patent application.

2. I received a Ph.D. in human genetics from the Graduate School of Public Health of the University of Pittsburgh in 1975. I joined the National Cancer Institute in 1981 and have held a variety of positions in the extramural Developmental Therapeutics Program relating

to the development and implementation of novel drug screening projects for the treatment of cancer and AIDS. In 1999, I was appointed Chief of the Antiviral Evaluations Branch, a position that has evolved into my present position as Chief of the Screening Technologies Branch. My field of research is the identification and exploitation of molecular targets for drug discovery, development of clinically relevant methods for target monitoring, and natural products-based drug discovery. A copy of my CV is provided as Exhibit A.

3. It is my understanding that the Examiner has rejected claims 1, 2, 7, and 9-17 as allegedly not enabled by the specification because although the specification provides exemplary data showing *in vitro* activity of the claimed compounds, no data are presented in the examples to illustrate the activity of the compound *in vivo*. This Declaration provides additional data as further evidence that the specification enables one of ordinary skill in the art to use the compounds *in vivo* to inhibit proliferation of a human immunodeficiency virus.

4. An exemplary compound having a structure as claimed was evaluated *in vivo* using the SCID-hu mouse model (McCune et al., *Science* 241:1632-1639 (1988)) that was developed for the study of HIV-1 pathogenesis *in vivo*. This model is constructed by transplantation of interactive human lymphoid organs into immunodeficient CB-17-scid mice. The SCID-hu model has been optimized by use of conjoint implants of human fetal thymus and liver to create the SCID-hu Thy/Liv mouse. These organs fuse, become vascularized, and grow when implanted beneath the kidney capsule, eventually reaching a total mass of 10^7-10^8 human cells in 80—90% of recipient mice (Namikawa et al., *J. Exp. Med.* 172:1055-1063 (1990)). A stable organ termed "Thy/Liv" is thus established with histologically normal cortical and medullary compartments that are capable of multilineage human hematopoiesis and generating a continuous source of human $CD4^+$ T cells for 6—12 months (Krowka et al., *J. Immunol.* 145:3751-3756 (1991); Namikawa et al., *J. Exp. Med.* 172:1055-1063 (1990); Vandekerckhove et al., *J. Exp. Med.* 176:1619–1624 (1992); Vandekerckhove et al., *J. Immunol.* 146:4173–4179 (1991)). The implants support viral replication after inoculation of HIV-1 by direct injection (Namikawa et al., *Science* 242:1684-1686 (1988)), and thymocyte depletion occurs with some

viral isolates within 3—5 weeks (Aldrovandi et al., *Nature* 363:732-736 (1993); Berkowitz et al., *J. Virol.* 72:10108-10117 (1998); Bonyhadi et al., *Nature* 363:728-732 (1993); Kaneshima et al., *J. Virol.* 68:8188-8192 (1994); Stanley et al., *J. Exp. Med.* 178:1151-1163 (1993)). This depletion includes loss of $CD4^+CD8^+$ immature cortical thymocytes and a decrease in the CD4/CD8 ratio in the thymic medulla. Administration of nucleoside (AZT, ddl, 3TC) and nonnucleoside (nevirapine) reverse transcriptase inhibitors to these mice results in dose-dependent inhibition of HIV-1 replication (and protection of $CD4^+$ cells) within the implanted human tissue (Namikawa et al., *Science* 242:1684-1686 (1988); Stanley et al., *J. Exp. Med.* 178:1151-1163 (1993); Stoddart et al., *Antimicrob. Agents Chemother.* 42:2113–2115 (1998)). The model has been also used to evaluate new classes of HIV-1 inhibitors, such as bicyclam (Datema et al., *Antimicrob. Agents Chemother.* 40:750-754 (1996)) and oligonucleotide (Stoddart et al., *Antimicrob. Agents Chemother.* 42:2113–2115 (1998)) inhibitors of HIV-1 entry, the nucleoside analog dOTC (Stoddart et al., *Antimicrob. Agents Chemother.* 44:783–786 (2000)), and an oxime-piperidine CCR5 antagonist (Strizki et al., *Proc. Natl. Acad Sci. USA* 98:12718-12723 (2001)).

5. The data presented in this Declaration were obtained using a representative pentavalent antimony-containing small molecule of the invention (designated NSC 13778). The compound has an EC_{50} of 1 μM and selectivity index of greater than 426 in CEM-SS cells infected with the HIV-1 isolated RF. A toxicity study of NSC-13778 in the mouse model demonstrated that twice-daily subcutaneous injections of NSC 13778 at 2-60 mg/kg/day for 21 days caused no apparent toxicity or body weight loss (Figure 1, provided in Exhibit B). Treatment also did not cause thymocyte depletion or perturbations in thymocyte subpopulations except for a minor decrease in CD4/CD8 ratio (from 2.9 to 2.0) at 60 mg/kg/day.

6. A total of 45 mice were evaluated in the antiviral efficacy experiments described here. Thy/Liv mice were inoculated with HIV-1 by direct injection of 1,250 $TCID_{50}$ into each Thy Liv/implant. Mice were divided into seven groups (A-G) of seven animals each. Group A through F mice were inoculated with virus and group G mice were mock-inoculated. Groups A, B, and C were treated with NSC 13778. The drug 3TC was administered to animals

in group D as a positive control (it is known to inhibit HIV-1 viral infection); vehicle alone (group E) was used as a negative control. Mice in groups F and G were not treated with either drug or vehicle. All mice were dosed by subcutaneous injection (150 μL per dose) twice-daily throughout the treatment course. The amounts administered were: 60 mg/kg/day NSC13778 (group A), 20 mg/kg/day NSC13778 (group B), 6 mg/kg/day NSC13778 (group C), 30 mg/kg/day 3TC (group D), and vehicle only, 0.05 M NaOH, (group E). Groups A-G were treated for 1 day, inoculated with virus or mock-inoculated and subsequently treated for 21 days, all as described above. At the end of the 21 days of treatment, Thy/Liv implants were surgically excised from mice in groups A through G in order to examine the effect of NSC 13778 on HIV-1 replication by measuring levels of p24-Gag and HIV-1 RNA. Three mice (one in group B, one in group C, and one in group F) were not used because of poor implant quality or lack of implant. One of the mice in group G was excluded from all implant analyses because of an abnormal cell profile.

7. Post-excising, implant thymocyte samples containing 10^6 cells were pelleted and either lysed for Gag-p24 analysis or stored and subsequently processed by standard methods for RNA isolation and analysis. The levels of p24 were measured by standard ELISA protocols and expressed as pg per 10^6 implant thymocytes. The levels of RNA were detected using the VERSANT™ HIV-1 RNA 3.0 Assay (Bayer Diagnostics, Norwood, Massachusetts) and expressed as RNA copies per 10^6 implant thymocytes. MHC class I detection was performed using fluorescently labeled anti-CD4, anti-CD8, anti-CD3 and anti-CD195 antibodies in a standard FACS analysis.

8. Untreated, HIV-1 infected mice (Group E) had means of 590 ± 87 pg p24 and 5.8 ± 0.15 $\log_{10}$ copies HIV-1 RNA per 10^6 implant cells and 8.6 ± 1.1% Gag-$p24^+$ thymocytes at 21 days after inoculation. These untreated mice also exhibited a 3.1-fold increase in MHC class I expression on $CD4^+CD8^+$ immature cortical thymocytes. Substantial reductions in $CD4^+CD8^+$ thymocytes (from 82% to 33%), CD4/CD8 ratio (from 1.7 to 0.67) and thymocyte viability (from 83% to 52%) in infected compared to mock-infected implants also were observed at 21 days after virus inoculation.

9. Thy/Liv mice that were treated with NSC 13778 at 60 mg/kg/day exhibited statistically significant reductions in p24, from 590 to 210 pg p24 per 10^6 cells (Figure 2, provided in Exhibit B). The 60 mg/kg/day treatment also reduced the HIV-1 viral RNA from 5.8 $\log_{10}$ to 4.9 $\log_{10}$ copies per 10^6 cells and Gag-$p24^+$ thymocytes from 8.6% to 4.9% as compared to non-NSC 13778 treated, HIV-1 infected controls (also Figure 2), however, there were no significant reductions in MHC class I expression on $CD4^+CD8^+$ thymocytes from NSC 13778-treated mice compared to implants from untreated, HIV-1 infected control mice. Treatment with NSC 13778 did not protect thymocytes from virus-mediated depletion.

10. These data show dose-related inhibition of viral replication in response to treatment with NSC 13778 as assessed by p24 viral core antigen levels and HIV RNA levels (Figure 2). These experiments therefore provide additional evidence that the specification enables one of ordinary skill in the art to use the compound of the invention *in vivo* to inhibit proliferation of a virus.

11. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon.

Dated: 2/28/08

Robert H. Shoemaker, Ph.D.

Exhibit A

February 2008

CURRICULUM VITAE

Robert H. Shoemaker, Ph.D.

EMPLOYMENT ADDRESS:
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Frederick, Maryland 21702-1201

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FAX: 301-846-6844
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EDUCATION:

1971 B.S., College of Arts and Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania

1973 M.S. in Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania

1975 Ph.D. in Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania

EMPLOYMENT:

Research Assistant, Cytogenetics Laboratory, Department of Radiation Health, University of Pittsburgh, Pittsburgh, Pennsylvania, October, 1972-April, 1973.

Research Associate, Shadyside Hospital Institute of Pathology, Pittsburgh, Pennsylvania, May, 1973-September, 1973.

Chief, Experimental Pathology, Shadyside Hospital Institute of Pathology, Pittsburgh, Pennsylvania, September, 1973-April, 1975.

Captain, Medical Service Corps, U.S. Army, assigned to the Department of Cellular Pathology, Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D.C.,July, 1975-May, 1977.

EMPLOYMENT:
Senior Research Associate, Department of Pathology, Children's Hospital Medical Center of Akron, Akron, Ohio; Consultant, Genetics Clinic, Children's Hospital Medical Center of Akron, June, 1977-November, 1981.

Acting Head, Cell Culture Section, Drug Evaluation Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, November, 1981-February, 1985.

Head, Cell Culture Section, Drug Evaluation Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, February, 1985-April, 1986.

Special Assistant for Research and Development, Office of the Associate Director, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD, April, 1986-February, 1988.

Acting Chief, Information Technology Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, February, 1988-July, 1989.

Special Assistant for Research and Development, Office of the Associate Director Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute National Institutes of Health, Bethesda, MD, July, 1989-February 1990.

Senior Investigator, Cell Biology, Biochemistry, and Experimental Therapeutics Section, Laboratory of Drug Discovery Research and Development, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Frederick Cancer Research and Development Center, February, 1990-February, 1994.

Acting Head, Cell Biology, Biochemistry, and Experimental Therapeutics Section Laboratory of Drug Discovery Research and Development, Developmental Therapeutics Program Division of Cancer Treatment, National Cancer Institute Frederick Cancer Research and Development Center, February, 1994-February 1995.

Head, Biology Section, Laboratory of Drug Discovery Research and Development, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Frederick Cancer Research and Development Center, February, 1995-February, 1996.

Senior Investigator, Discovery Section, Laboratory of Drug Discovery Research and Development, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute, Frederick Cancer Research and Development Center, February, 1996-August, 1999.

EMPLOYMENT:
Acting Chief, Antiviral Evaluations Branch, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis, National Cancer Institute, Bethesda, Maryland, February, 1998-August, 1999.

Acting Chief, Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis, National Cancer Institute, Bethesda, Maryland, August, 1999-June, 2000.

Chief, Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis, National Cancer Institute, Bethesda, Maryland, June, 2000-present.

COMMITTEE APPOINTMENTS (Selected Listing):
Member, Drug Evaluation Committee, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1981-1985.

Member, Biological Evaluation Committee (Cancer), Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1985-1989.

Member, Decision Network Committee, Division of Cancer Treatment, National Cancer Institute, 1987-1989.

Member, Drug Screening Acquisitions and Input Committee, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1988-1989.

Member, Operating Committee, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1988-1989.

Member, Developmental Therapeutics Program Senior Staff Contract Review Committee, National Cancer Institute, 1988-1989.

Member, Biological Evaluation Committee (AIDS), Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1987-1989.

Member, AIDS In Vivo Models Committee, AIDS Program, National Institute of Allergy and Infectious Diseases, 1988-1989.

Scientific Program Committee, 9th NCI-EORTC Symposium on New Drugs in Cancer Therapy, Amsterdam, The Netherlands, 1995.

Member, Thesis Examination Committee (doctoral thesis of Miguel A. Izquierdo, M.D.), Free University of Amsterdam, The Netherlands, February, 1996.

COMMITTEE APPOINTMENTS (Selected Listing):
Member, National Institutes of Health Inter-Institute Working Group on Hepatitis C, February 1998-2000.

Scientific Program Committee, 14th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Frankfort, Germany, November, 2002.

Member, Radiation Modifier Working Group of the National Cancer Institute, 2002.

Scientific Program Committee, 16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Geneva, Switzerland, September, 2004.

LECTURES PRESENTED AT MAJOR SYMPOSIA (Selected Listing)
Speaker, Third Conference on Human Tumor Cell Cloning, Tucson, AZ, January, 1981.

Invited Speaker, 13th International Cancer Congress, Seattle, WA, September 8-15, 1982

Speaker, US-Japan Eighth Annual Treatment Program Area Review Meeting, Bethesda, Maryland, November 22-24, 1982.

Organizer, Chairman, and Speaker, National Cancer Institute Symposium: "Cellular Resistance to Anti-Cancer Drugs", Bethesda, Maryland, February 25, 1983.

Invited Speaker, US-Japan Joint Seminar on Anticancer Drug Resistance, Honolulu, HA, May 30 - June 1, 1983.

Invited Speaker, National Cancer Institute Symposium: "Discovery and Development of Naturally Occurring Antitumor Drugs", Frederick, Maryland, June 27-29, 1983.

Invited Speaker, Fourth Conference on Human Tumor Cloning, Tucson, AZ, January 8-10, 1984.

Invited Lecture, 12th International Chemotherapy Congress, Vienna, Austria, 1984.

Invited Lecture, Symposium on Drug Discovery, Behringwerke, Marburg, West Germany, 1984.
Co-organizer (with Dr. Michael Boyd) and Speaker, NCI Workshop on "Disease-Oriented Antitumor Drug Discovery and Development", Bethesda, Maryland, January 9-10, 1985.

Invited Speaker, Early Clinical Trials - Preclinical Screening and Pharmacokinetic Group Meetings of the European Organization for Research and Treatment of Cancer (EORTC), Lugano, Switzerland, May 31, 1985.

LECTURES PRESENTED AT MAJOR SYMPOSIA (Selected Listing)

Session Co-Chairman (with Dr. Takashi Tsuruo) and Speaker, Symposium on "Resistance to Anticancer Drugs", 14th International Chemotherapy Congress, Kyoto, Japan, June 23-28, 1985.

Invited Lecture, International Union Against Cancer (UICC) - Study Group Meeting, Oslo, Norway, September, 9-11, 1985.

Invited Lecture, Seminar on Human Tumor Xenografts in Anticancer Drug Development, European School of Oncology, Stelline Palace, Milan, Italy, May 26-27, 1986.

Invited Speaker, European Organization for Research and Treatment of Cancer (EORTC) Clonogenic Assay Screening Study Group Meeting, Nijmegan, The Netherlands, June 2-4, 1986.

Invited Lecture, FASEB Summer Conference on "Lung Pharmacology", Saxton's River, Vermont, July 28 - August 1, 1986.

Invited Speaker, First Beijing International Symposium on "Cancer Treatment and New Trends of Cancer Chemotherapy", Beijing, People's Republic of China, September 7-9, 1986.

Invited Speaker, Biochemical Modulators Advisory Group - NCI Phase I Clinical Trials Working Group Meeting, Bethesda, Maryland, November 17, 1986.

Co-organizer (with Dr. Michael Boyd) and Speaker, NCI/NIAID Workshop on "Issues for Implementation of a National Anti-HIV Preclinical Drug Evaluation Program: Critical Parameters for an In Vitro Human Host-Cell Based, Primary Screen", Rockville, Maryland, April 8-9, 1987.

Co-organizer (with Dr. Michael Boyd) and Speaker, NCI Workshop, "Issues Concerning Selection, Characterization and Quality Control of Human Tumor Cell Lines for the National Cancer Institute's New Drug Screening Program", Bethesda, Maryland, May 27-28, 1987.

Invited Lecture, 57th ANZAAS Congress, James Cook University of North Queensland, Townesville, Australia, August 28, 1987.

Invited Speaker, "Horizons on Antibiotic Research", Memorial Symposium Dedicated to Professor Hamao Umezawa, Tokyo, Japan, November 25-26, 1987.

Invited Lecture, Gordon Research Conference, "Mechanisms of Toxicity", Kimball Union Academy, July, 1989.

Co-chairman (with Dr. Emil Frei) and Speaker, Round-table Session: "Discovery, Evaluation, and Development of Anticancer Drugs", International Cancer Congress, Hamburg, Germany, August 22, 1990.

LECTURES PRESENTED AT MAJOR SYMPOSIA (Selected Listing)

Invited Speaker, International Symposium on Cytostatic Drug Resistance, Kiel, Germany, November, 1991.

Co-chairman (with Peter Buhl Jensen, M.D.) and invited speaker, Preclinical Drug Development Session, Second Nordic Symposium on Lung Cancer, Sorrento, Italy, August, 1995.

Co-Chairman (with Alex Matter, M.D.), Session on New Trends in Cell and Animal Screening Models, 10th NCI-EORTC Symposium on New Drugs in Cancer Therapy, Amsterdam, The Netherlands, June, 1998.

Invited Faculty, Graduate Course on "Preclinical and Clinical Pharmacodynamics of Anticancer Agents", Oncology Graduate School of Amsterdam, December, 1998.

Invited Speaker, British Cancer Research Meeting, Leeds, UK, June, 2001.

Invited Speaker, 7th International Symposium on Cancer Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Tokyo, Japan, December, 2002.

Invited Speaker, EORTC Pharmacology and Molecular Mechanisms Group Meeting, Copenhagen, Denmark, January, 2002.

Keynote Speaker, British Association for Cancer Research, Special Conference "Cancer Drug Discovery: the molecular target/chemistry interface", Oxford, UK, September 8-10, 2002.

Invited Speaker, 8th International Symposium on Cancer Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Tokyo, Japan, December, 2003.

Invited Speaker, Gordon Research Conference on Molecular Therapeutics of Cancer, Colby-Sawyer College, New London, NH, July, 2004.

Invited Speaker, symposium on the "Chemistry Biology Interface: Synergistic New Frontiers", New Delhi, INDIA, November 2004.

Invited speaker, EORTC Pharmacology and Molecular Mechanisms Group Meeting, Berlin, 2007.

ACADEMIC APPOINTMENTS:

Instructor of Anatomy (Histology), Uniformed Services University of the Health Sciences, School of Medicine, Bethesda, Maryland, October, 1976 - May, 1977.

Lecturer in Biology (Genetics), the University of Akron, Akron, Ohio, Fall, 1979.

Assistant Professor of Experimental Pathology, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio, July, 1978-November, 1981.

AWARDS:
United States Public Health Service Traineeship, Academic Year 1974-1975, Grant Number 5 Tol Es0017-07.

Joint Service Commendation Medal for Service at the Armed Forces Institute of Pathology, awarded June 30, 1977.

National Institutes of Health Merit Award, shared with Dr. Michael Currens, "For design, implementation, and management of novel drug screens for AIDS and opportunistic infection-related targets", 2001.

PROFESSIONAL CERTIFICATION:
Board Certified, American Board of Medical Genetics, Medical Geneticist Specialty, 1982.

EDITORIAL BOARD MEMBERSHIP:
Journal of the National Cancer Institute, 1992-present
Journal of Molecular Medicine, September 2004-present
Cancer Science (formerly Japanese Journal of Cancer Research – Gann), 2004 – present
Journal of Experimental Therapeutics and Oncology, 1995- present
Oncology Reports, 1994-1997
Stem Cells (formerly International Journal of Cell Cloning), 1986-1993
Invasion and Metastasis, 1990-1995

PROFESSIONAL AFFILIATIONS:
American Association for Cancer Research

MILITARY STATUS:
Lt. Colonel, Medical Service Corps, U.S. Army Reserve (Retired).

Principal or Co-Principal Investigator for Government Collaborative Research and Development Agreements (CRADAs):

Phytobiotech, Inc., Laval, Canada: Identification of Novel Antitumor and Antimicrobial Agents Through Screening of Naturally-Derived Phytochemical Libraries

University of Pennsylvania (Robert Ricciardi, Ph.D.), MTA-CRADA: Targeted-Screening for Inhibitors of Human Herpesvirus 8 DNA Polymerase

Principal or Co-Principal Investigator for Government Collaborative Research and Development Agreements (CRADAs):

ChemBridge Corporation, San Diego, California, MTA-CRADA: Supply of Chemical Libraries for Use in Targeted-Screening for Inhibitors of Human Hepesvirus 8 DNA Polymerase

Albany Molecular Research, Inc., Albany, NY: Utilization of BIOACTIV™ for the development of Compound Derivatives

Novuspharma, Milan, Italy: Development of inhibitors of the Hypoxia Inducible Factor (HIF-1) Transcriptional Activation Pathway

TopoTarget, Copenhagen, Denmark: Clinical Evaluation of PDX-101, a Novel HDAC Inhibitor and Development of Second Generation HDAC Inhibitors

Merlion Pharmaceuticals, Singapore: Screening of MerLion's Natural Products for Novel Small Molecule Inhibitors of the Hypoxic Signaling Pathway (CRADA # 02069)

Sigma Tau Industrie Farmaceutische Riunite S.p.A., Milan, Italy: Evaluation of Topoisomerase I Inhibitors as Antitumor Inhibitors of Hypoxia Inducible Factor 1 (M-CRADA # 01893)

PATENTS:

Pommier Yves; Shoemaker, Robert H.; Scuidero, Domonic; Currens, Michael; Cardellina, John; Jobson, Andrew. Use of Chk2 kinase inhibitors for cancer treatment. PCT Int. Appl. (2007) WO 2007016338

Sei, Shizuko; Marquez; Victor; Shoemaker, Robert H.
North-2'-deoxy-methanocarbathymidines as antiviral agents for the treatment of Karposi's sarcoma-associated herpes virus and for the treatment of Karposi's sarcoma. PCT Int. Appl. (2006), WO 2006113204

Shoemaker, Robert H.; Currens, Michael; Rein, Alan; Feng; Ya-Xiong; Fisher, Robert; Stephen, Andrew; Worthy, Karen; Sei, Shizuko; Crise, Bruce; Henderson, Louis E.
Stibonic acid compounds and diphenyl compounds for inhibiting viral replication. PCT Int. Appl. (2004) WO 2004032869

Boyd, Michael R.; Gustafson, Kirk R.; Shoemaker, Robert H.; McMahon, James B.;
Isolation, cloning and sequence of antiviral cyanovirin-N proteins and peptides from Nostoc ellipsosporum. U.S. (1998) Cont.-in-part of U.S. Ser. No. 429, 965 US 5821081

Boyd, Michael R.; Gustafson, Kirk R.; Shoemaker, Robert H.; McMahon, James B.
Antiviral cyanovirin proteins, synthetic DNA coding sequences for its recombinant production and activity against HIV-1 virus. PCT Int. Appl. (1996) WO 9634107

BIBLIOGRAPHY

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2. Fisher, E.R., Wholey, M., and Shoemaker, R.H. Cigarette Smoking and Cholesterol Atherosclerosis of Rabbits. Archives of Pathology 98: 418-421, 1974.

3. Fisher, E.R., Shoemaker, R.H., and Sabnis, A. Relationship of Hyperplasia to Cancer in MCA-Induced Mammary Tumorogenesis. Laboratory Investigation 33: 33-42, 1975.

4. Fisher, E.R., Shoemaker, R.H., and Palekar, A.S. Identification of Premalignant Hyperplasia in Methylcholanthrene Induced Mammary Tumorogenesis. Laboratory Investigation 33: 446-450, 1975.

5. Shoemaker, R.H. X Chromatin and Aging. Acta Cytologica 21: 127-131, 1977.

6. Fletcher, R.D., Shoemaker, R.H., and Albertson, J.N. Desmosomes Observed in a Gingival Cell Line. Journal of Dental Research 56: 1106, 1977.

7. Lake, R.S., Kropko, M.L., Pezzutti, M.R., Shoemaker, R.H., and Igel, H.J. Chemical Induction of Unscheduled DNA Synthesis in Human Skin Epithelial Cell Cultures. Cancer Research 38: 2091-2098, 1978.

8. Lake, R.S., Kropko, M.L., McLachlan, S., Pezzutti, M.R., Shoemaker, R.H., and Igel, H.J. Chemical Induction of DNA Repair Synthesis in Human Peripheral Blood Monocytes. Mutation Research 74: 357-377, 1980.

9. Shoemaker, R.H., Abbott, B.J., Macdonald, M.M., Mayo, J.G., Venditti, J.M., and Wolpert-DeFilippes, M.K. Use of the KB Cell Line for In Vitro Cytotoxicity Assays. Cancer Treatment Reports 67: 97, 1983.

10. Shoemaker, R.H., Wolpert-DeFilippes, M.K., and Venditti, J.M. Application of a Human Tumor Clonogenic Assay to Screening for New Antitumor Drugs. Proceedings of the 13th International Congress of Chemotherapy, 223/14-223/19, 1983.

11. Shoemaker, R.H., Curt, G.A., and Carney, D.N. Evidence for Multi-Drug Resistant Cells in Human Tumor Cell Populations. Cancer Treatment Reports 67: 883-888, 1983.

12. Shoemaker, R.H., Wolpert-DeFilippes, M.K., and Venditti, J.M. Potentials and Drawbacks of the Human Tumor Stem Cell Assay. Behring Institute Mitteilungen 74: 262-272, 1984.

13. Shoemaker, R.H., Wolpert-DeFilippes, M.K., Melnick, N.R., Venditti, J.M., Simon,R.M., Kern, D.H., Lieber, M.M., Miller, W.T., Salmon, S.E., and Von Hoff, D.D. Recent Results of New Drug Screening Trials with a Human Tumor Colony Forming Assay. In: Human Tumor Cloning, S. Salmon and J. Trent (Eds.), Grune & Stratton, Orlando, Florida, 1984, pp. 345-355.

14. Weisenthal, L.M., Shoemaker, R.H., Marsden, J.A., Dill, P.L., Baker, J.A., and Moran, E.M. In Vitro Chemosensitivity Assay Based on the Concept of Total Tumor Cell Kill. Recent Results in Cancer Research 94: 161-173, 1984.

15. Shoemaker, R.H., Wolpert-DeFilippes, M., Kern, D., Lieber, M., Makuch, R., Miller, W., Salmon, S., Venditti, J., and Von Hoff, D. Application of a Human Tumor Colony Forming Assay to New Drug Screening. Cancer Research 45: 2145-2153, 1985.

16. Marsh, J.M., Shoemaker, R.H., and Suffness, M. Stability of the In Vivo P388 Leukemia Model in Evaluation of Antitumor Activity of Natural Products. Cancer Treatment Reports 69: 683-685, 1985.

17. Shoemaker, R.H. New Approaches to Antitumor Drug Screening: The Human Tumor Colony Forming Assay. Cancer Treatment Reports 70: 9-12, 1986.

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19. Taetle, R., Honeysett, J. M., Rosen, F., Shoemaker, R. H. Use of Nude Mouse Xenografts as Preclinical Drug Screens: Further Studies on In Vitro Growth of Xenograft Tumor-Colony Forming Cells. Cancer 58: 1969-1978, 1986.

20. Shoemaker, R., Wolpert-DeFilippes, M., Plowman, J., Abbott, B., Venditti, J., Trader, M., Griswold, D., Gerlach, J., and Ling, V. Pleiotropic Resistance and Drug Development. Progress in Clinical and Biological Research 223: 143-149, 1986.

21. Scheithauer. W., Clark, G.M., Salmon, S.E., Dorda, E., Shoemaker, R.H., and Von Hoff, D.D. A Model for Estimation of Clinically Achievable Plasma Concentrations for Investigational Anticancer Drugs in Man. Cancer Treatment Reports 70: 1379-1382, 1986.

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Exhibit B

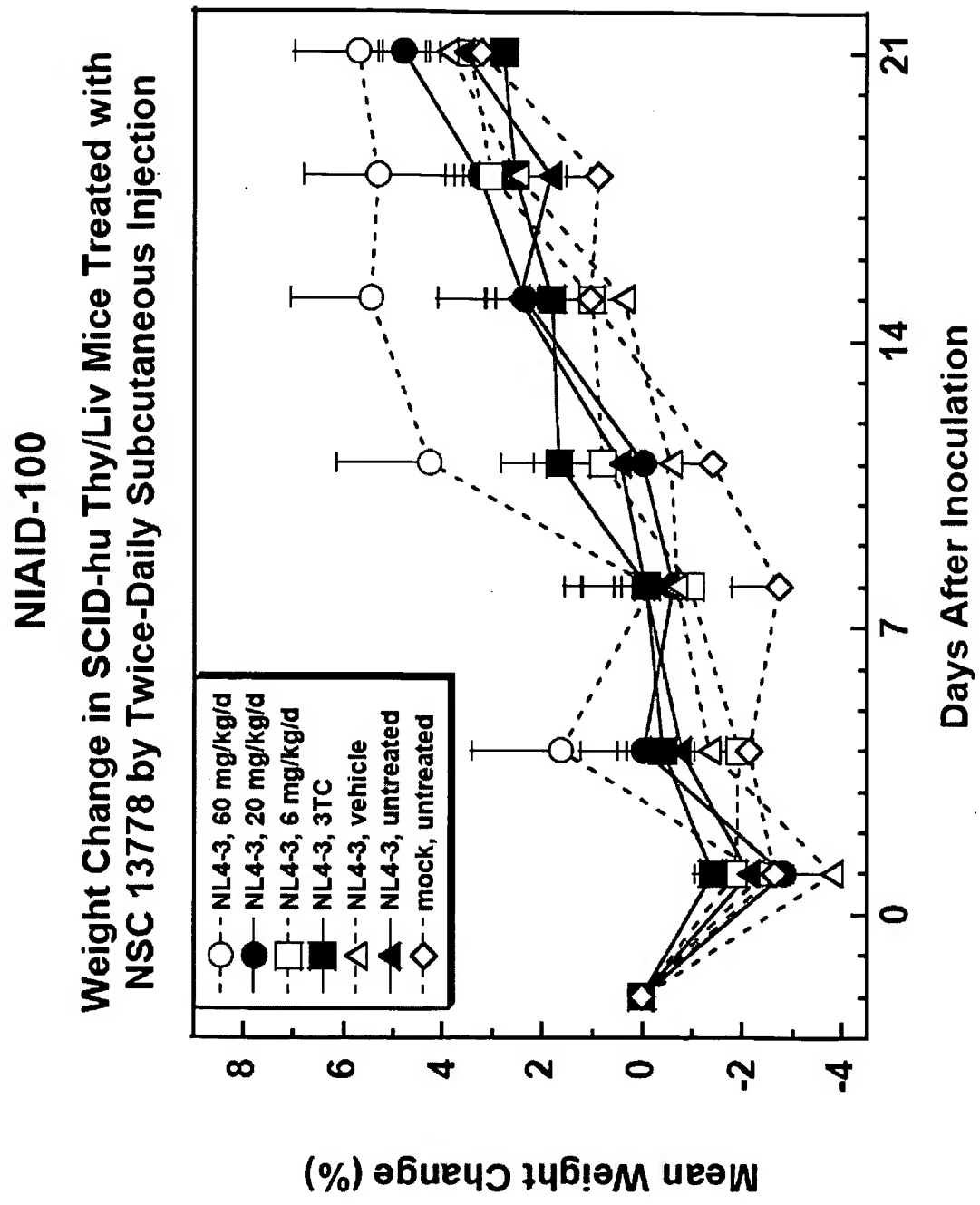

Exhibit B (figure 1)
Declaration Under 37 CFR 1.132 by Dr. Robert Shoemaker

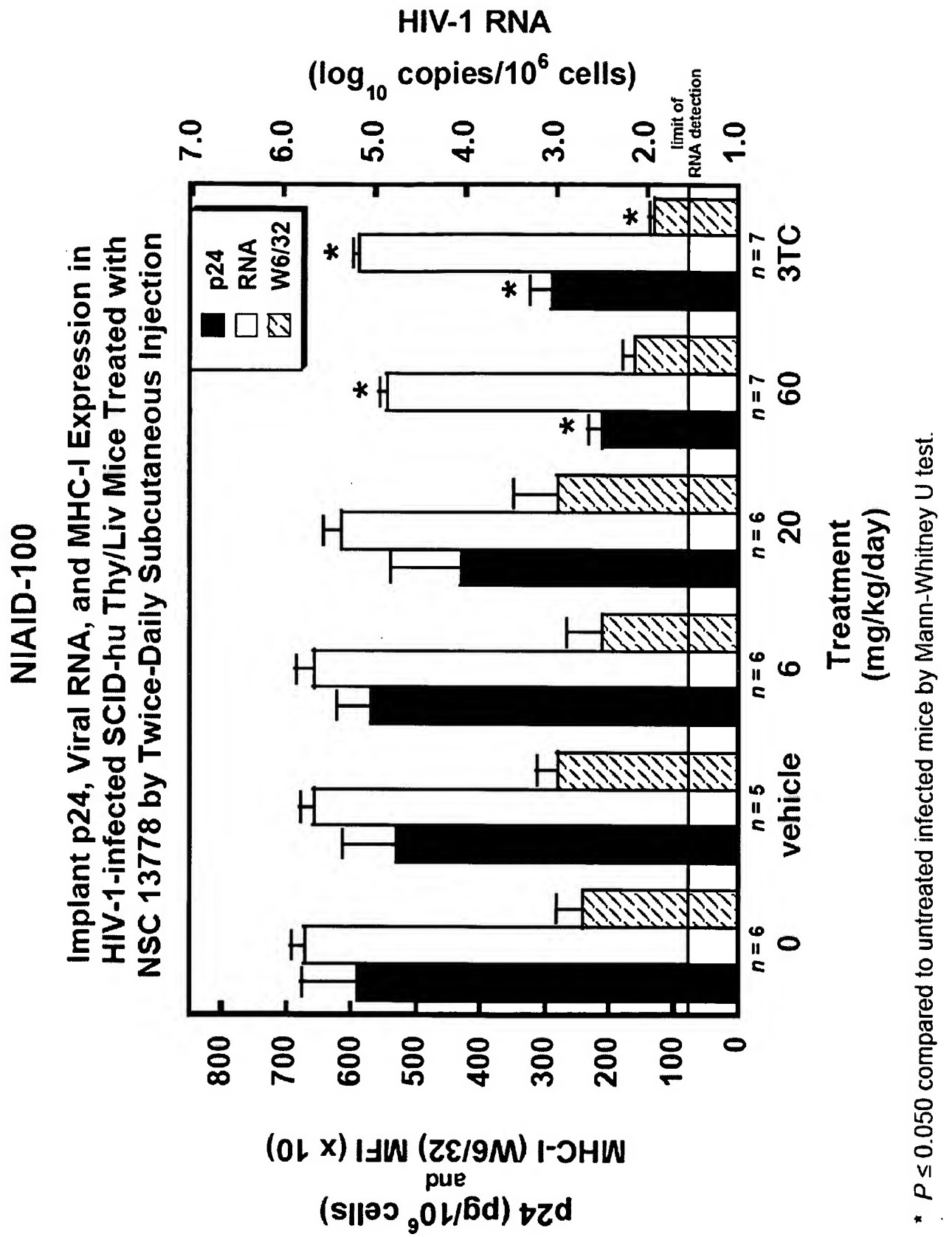

Exhibit B (figure 2)
Declaration Under 37 CFR 1.132 by Dr. Robert Shoemaker